UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

Office of Prevention, Pesticides and Toxic Substances

June 20, 2000

MEMORANDUM

SUBJECT: ***Dichlorvos*****:** Response to the Registrant's (AMVAC Chemical Company) Comments on the Revised Preliminary Risk Assessment

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On behalf of AMVAC Chemical Company, Bergeson & Cambell, P.C. submitted comments on the exposure, toxicology and risk assessment issues on dichlorvos (DDVP). The registrant disagrees with OPP's positions on the toxicology assessment of this chemical for the following reasons:

1. Dismissal of human data

2. Lack of review of pig studies and a rationale for the use of an FQPA factor of 3X
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3. Changing the toxicity value from a human acute study to a short-term animal study

4. The toxicological endpoints reported at 2.5 mg/kg/day in the rabbit developmental study

not in agreement with the study report.

5. Misinterpretations of data and gross errors in calculations based on Blair et al study.

In addition, the registrant noted errors in the revised Preliminary Risk Assessment Document (PRA). These along with Agency's responses are presented below.

Page 3: The registrant claims that the Agency raised a concern regarding potential of DDVP to affect the developing offspring based on a poorly conducted Mehl et al. study in guinea pig while ignoring the extensive literature on the developmental effects of DDVP and trichlorfon in the pig which contain quantitative information relevant to the risk assessment of DDVP (reference to AMVAC letter dated March 17, 2000). The registrant further stated that the PRA does not present the contrasting results between the effects of piglets treated with trichlorfon and those treated with DDVP. The Agency provides no rationale for reducing FQPA factor to 3 and not 1. This error is linked to the failure on the part of the Agency to review the pig literature on these compounds. In addition, the PRA states the range of uncertainty factors as 10 to 300 which is not in agreement with the listing of uncertainty factors on page 16.

EPA consideration: RRB4 reviewed the literature studies on the developmental effects of trichlorfon and presented them to the Hazard Identification Assessment Review Committee (HIARC) of HED, to determine an appropriate safety factor regarding the data gap. The pig studies on DDVP submitted by the registrant were reviewed, some of which were submitted only in an abstract form. A key point is that the slow-release formulation used in all of these studies is considerably different than "instant" release formulations and, for this reason, none of the DDVP studies can be used to negate the trichlorfon findings in pigs where "instant" release treatments were used. In one of the DDVP studies (Stanton et al), the acute toxicities of technical DDVP and the resin formulation were compared. The studies focus on a phenomenon noted in the 60's that treatment of sows for worms during the last 30-days of pregnancy with a DDVP-containing PVC resin resulted in improved reproductive performance. Reproductive performance in this instance means that there was a higher proportion of live births, piglets had a higher birth weight, and more were viable. Wrathall et al determined that the resin formulation of DDVP was not teratogenic to pigs at a comparatively low dose of 8.5 mg/kg. The authors, in comparing the teratogenic response of DDVP and trichlorfon, speculated that "...because a slow release preparation (PVC-DDVP) was used, the amount of active organophosphorus compound which reached the foetuses may have been negligible." There were miscellaneous deficiencies as follows:

- The registrant submitted no studies published after 1980 on DDVP effects in pigs.

- Pregnant sows treated with the DDVP resin formulation at the recommended dosage exhibited no clinical signs of toxicity although plasma and RBC cholinesterase were depressed. Young pigs treated with as little as 1 mg/kg of the resin formulation exhibited decreased cholinesterase

levels.

- Piglets born from treated sows did not exhibit plasma or RBC cholinesterase depression. Even when pregnant sows exhibited reductions of 82% plasma and 90% RBC cholinesterases, piglets exhibited no reductions in either cholinesterase. These studies were conducted on a DDVP resin and did not administer DDVP in the same form as other developmental studies and therefore, the effects could not be compared. The Agency will review the study if the registrant provides an appropriately conducted study on DDVP and will then reassess the FQPA factor. As clearly indicated on page 14 of the risk assessment document, the FQPA factor was reduced to 3X because: 1) the standard developmental and reproductive toxicity studies submitted to the Agency showed no indication of increased susceptibility of rats, mice, or rabbits to *in utero* and/or postnatal exposure to DDVP; and 2) the dietary (food and drinking water) non-dietary (residential) risk assessments will not underestimate the potential exposures for infants and children from the use of DDVP. RRB4 also reviewed the studies on trichlorfon in pigs and guinea pigs. These studies are not new to us and together (except for Mehl, et. al.) comprise the support for not fully removing the FQPA factor. The studies clearly show that there are developmental effects on the developing pig and guinea pig brain.

The discrepancy in reporting the uncertainty factors in Table 3 on page 16 will be corrected.

Page 11: The registrant pointed out that although the Agency and SAP have concluded the evidence of carcinogenicity to be suggestive, the entry on Table 2, page 10, for carcinogenicity in mouse is listed as evidence of carcinogenicity.

EPA consideration: The error will be corrected in the revised risk assessment document.

Page 11 and 16: The registrant noted that on page 11, the NOAEL for maternal toxicity is listed as 2.5 mg/kg/day and for developmental toxicity at 7 mg/kg/day. However, the value for maternal NOAEL is listed on page 16 as 0.1 mg/kg/day and therefore, contradicts with the NOAEL.

EPA consideration: The error on page 11 will corrected in the revised risk assessment document.

Page 12 and 13: The registrant stated that the information from the authors and laboratory regarding the Mehl et al. 1994 should be verified and added (reference to data submitted to EPA on January 19 and March 21, 2000). Regarding the discussion of studies submitted by AMVAC, the registrant noted several errors as follows: a) There were in excess of 100 studies submitted (and not 60 as reported on page 12); b) The studies were reported in such a manner indicating that old studies are inherently poor and new ones are inherently good This shows a bias not scientifically supported by the actual data; c) The PRA reported that the submitted studies do not demonstrate dose response and are not useful to quantify risk. This is incorrect.

Many studies contain quantitative information. Dose response is not needed for determining the relative sensitivity of man and animals. These studies demonstrate that both man and animals are equisensitive to the Cholinesterase-inhibiting properties of DDVP. In fact 30 studies taken together provide a compelling evidence of cholinesterase-inhibiting properties of DDVP. The registrant claimed that the Agency has ignored the extensive body of human data although it's present policy on the use of cholinesterase inhibition for risk assessments explicitly requires a consideration of all animal and human data, giving precedence to available human data. The Agency should use the weight of the evidence approach in the selection of endpoints for risk assessment based on human studies which will reduce the uncertainty factors. On page 13, the PRA states that the new data do not add any new information to the relevant animal database while in fact several studies (e.g., Tracy et al., 1960; Stanton et al., 1979; Wrathall et al., 1980 and Potter et al., 1973 being the most relevant) conducted to determine the developmental sensitivity of offspring and fetuses were not reviewed or mentioned by the Agency.

EPA consideration: The data submitted by the registrant were reviewed by RRB4 prior to presentation to HIARC. Based on this new information, the HIARC decided to change the recommendation from requesting guinea pig developmental study to rat developmental neurotoxicity study on DDVP. The revised HIARC report on DDVP and trichlorfon reflects the review of Mehl et al. study. Although the registrant submitted in excess of 100 studies, on page 12 the 60 studies the PRA refers to were exclusively toxicological studies. The studies although were relevant as far as ChE inhibition is concerned they were not useful to select an endpoint for risk assessment. Both human and animal studies submitted by AMVAC (February 11, 1999) were reviewed by HED. HED does not mean to imply that old studies are necessarily bad. However, the studies reviewed were not designed to set the NOAEL and LOAEL or to assess the dose-response. In the past, the Agency has used human studies to select an endpoint for risk assessment. Agency is now reassessing the use of human studies and the current Agency policy is that a regulatory decision cannot be made based on a human study until a formal decision has been made concerning the ethical aspects of such use. As this ethics decision regarding the use of toxicology studies employing human subjects has not been made, the HED has used a weight of the evidence approach for evaluation of ChE inhibition data to select the doses and endpoints to calculate dietary and non-dietary risk in the current assessment based solely on animal studies. The Agency will re-evaluate these studies to determine the acceptability after receiving the guidance from the Agency's Scientific Advisory Panel.

Page 14: According to registrant, under cancer classification, the item# 1 on page 14 of PRA, should indicate that the corn oil was the vehicle and it can suppress the spontaneous control values for MCL. There was no dose-related increase in MCL and the values in DDVP-treated animals were comparable to controls.

EPA consideration: An Hoc Cancer Assessment Review Committee (CARC) reviewed the Blue

Ribbon Panel Report. The data on the corn oil and untreated historical controls were presented to the full CARC Committee. Based on the review of this report (refer to attachments 1 and 2 to the sixth review), the CARC concluded that MCL in male F-344 rat has limited usefulness for human risk assessment. This is reflected in the summary of the sixth carcinogenicity review of DDVP.

Page 16: The registrant claims that the NOAEL in the acute neurotoxicity study in rats should not be treated as a LOAEL and the additional factor 3X factor should not be added. The use of human study would reduce the uncertainty factor of 3X. Acute studies typically measure clinical observations as the toxicological endpoint. There is no evidence to support using subtle cholinesterase inhibition.

EPA consideration: The HIARC reassessed the endpoints selected for risk assessment for short-term risk scenario and determined that the short-term animal study was more appropriate instead of acute human study because of Agency's current lack of policy on the use of human data. The Agency's current policy is that ChE inhibition can be used as an endpoint for risk assessment. A FIFRA uncertainty factor of 3X was applied because the ChE inhibition was not measured.

Page 16 & 17: The registrant contended that the of 2.5 mg/kg/day for maternal toxicity on page 11 is in disagreement with the discussion on page 17. Neither body weight nor clinical observations were affected at 2.5 mg/kg/day. Furthermore, the study is not designed to measure short-term toxicity. Clinical observations were noted only at 7 mg/kg/day . In addition, rabbits are not good indicator of toxicity and are not considered to be useful for measurement of repeat dose toxicity. In fact adequate human data exist to determine a NOAEL for ChE inhibition following short-term exposure to DDVP.

EPA consideration: HED has evaluated the rabbit developmental study and the Data Evaluation Report clearly states that administration of DDVP to NZW rabbits from gestation 7 through 19 resulted in maternal toxicity at 2.5 mg./kg/day and above, which was manifested as increased incidence of mortality, clinical cholinergic signs, and decreased body weight gain during the dosing period. Treatment-related decrease in body weight gain during GD 7-19 (approx. 12 days) was noted at 2.5 mg/kg/day which was determined to be the LOAEL for maternal toxicity. In addition, a significant reduction in corrected body weight gain, treatment-related cholinergic signs and mortality were observed at the next higher dose level, 7 mg/kg/day. Although the short-term exposure scenario covers the duration of 1-7 days, in the absence of another appropriate study, effect seen over 12 days was considered appropriate for risk assessment. As stated earlier, because of Agency's current lack of policy on the use of human data, an animal study was used in selecting an endpoint for risk assessment.

Page 18: The registrant noted that the target MOE for chronic inhalation exposure scenario is given as 100 (or as 30 in the previous sentence) which is in disagreement with the MOE given

on pages 6 and 47.

EPA consideration : During HIARC meeting on July 26, 1999, the Committee recommended using a NOAEL=0.00005 mg/L from a 2-year rat chronic inhalation study by Blair, et al. (1976) and an uncertainty factor of 30 (10X for intra species variation and 3X for interspecies variation) to calculate the risk for the intermediate-term and long term inhalation exposure scenarios. Agency's RfD/RfC Work Group used additional 3X to account for lack of reproduction study. This datagap is now fulfilled. Therefore, this dose/endpoint/study is appropriate for this exposure route and period of concern, and has been used to derive the Reference Concentration (RfC) by the Agency RfD/RfC Work Group. Table 3 in the PRA will be revised to reflect these changes.

Cc: Ray Kent/Branch Chief, RRB4